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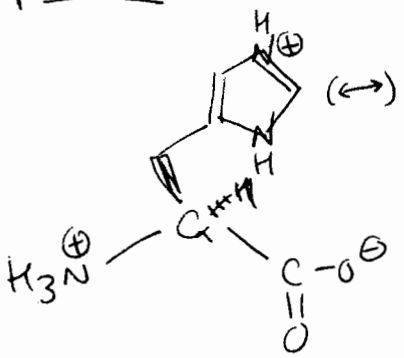
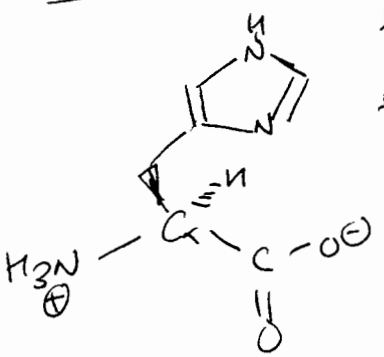
1. pH, pK_a, and all that (25 pts):

(a; 9 pts) The imidazole side chain of histidine has a pK_a of 6.04 (referring to the protonated side chain). Draw the dominant prototropic forms of histidine at (1) pH 4, (2) pH 8, and (3) pH 12.

pH 4

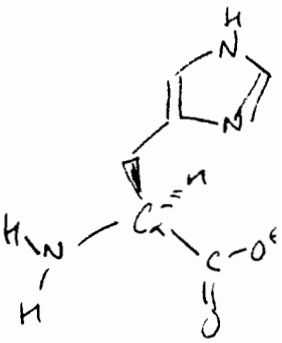


pH 8



this is the correct tautomer – but either is fine

pH 12



(+1) for an amino acid
(+2) for histidine side chain
(+2) for each correct protonation state (=6)
↳ i.e. all three correct at a given pH

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(b; 6 pts) Calculate the ratio of neutral to protonated histidine at pH 6.5.

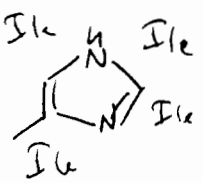
$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ (+1)

Here,

$$6.5 = 6.04 + \log \frac{[His]}{[HisH^+]}$$ (+3)

$$\log \frac{[His]}{[HisH^+]} = 0.46 \qquad \frac{[His]}{[HisH^+]} = 10^{0.46} = 2.88$$ (+2)

(c; 10 pts) We have mentioned that the pK_a of an amino acid side chain can change substantially in different protein contexts. If a histidine side chain were found buried among isoleucines in the center of a protein, what effect would this have on the actual pK_a of that particular side chain, and why? What if there were a buried aspartate as well?



- The hydrophobic environment will favor the neutral form of histidine. The charge side chain would much rather be in H_2O. (+3) (+2 for hydrophobic of charge)

- Therefore $HisH^+$ will become a stronger acid, corresponding to a lower pKa, larger $([His]/[HisH^+])$. (+3)

- A neighboring negatively charged aspartate, in contrast, will strongly stabilize $HisH^+$, and the pKa will increase. (+2 for opposite)

[The pKa of the Asp would ↑ if it were considered alone [+1 if correct, or +2 if other pKa missed]

2. Amino acid and peptide bond structure and chemistry (26 pts):

(a; 6 pts) Name the two sulfur-containing amino acids, and very briefly list one unique function for each.

Cysteine (+1) and methionine (+1) → (+2) initiation of protein biosynthesis, as f-Met

↳ Disulfide crosslinks (+2)

+1 for either one for protein radiolabeling

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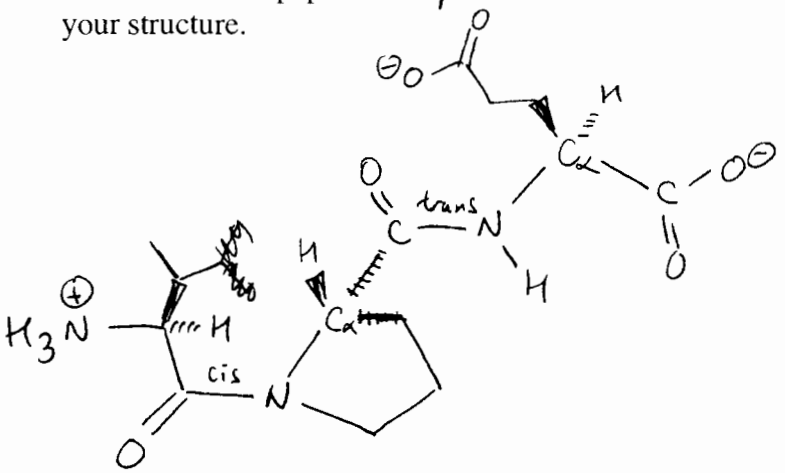
(b; 15 pts) Draw the structure of Valine-Proline-Glutamate at pH 7. Make the proline peptide bond *cis* and the other peptide bonds *trans*. Give the 3- and 1-letter codes for each amino acid below your structure.



Val Pro Glu

V P E

(+2) for any tripeptide

(+2) for each side chain = 6

(+2) for cis peptide bond

(+1) for ⊖ charge on Glu

(+1) for charges on both terminii correct

(+1) for each correct pair of labels = 3

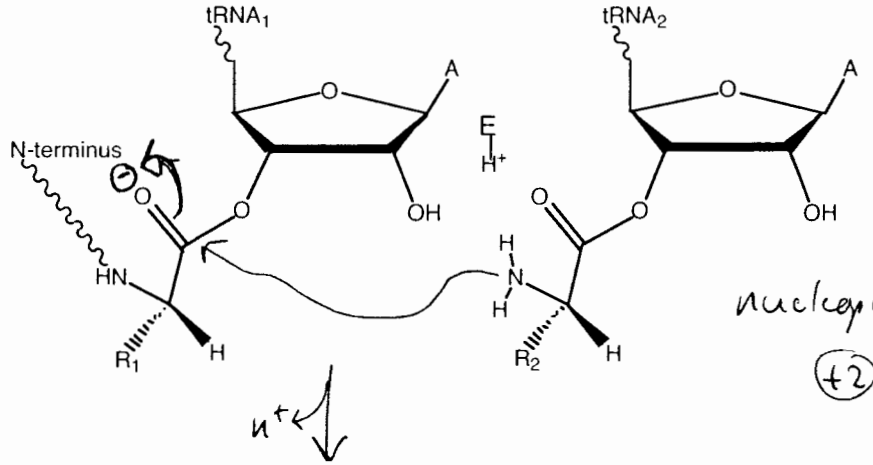
15

Stereochemistry not graded.

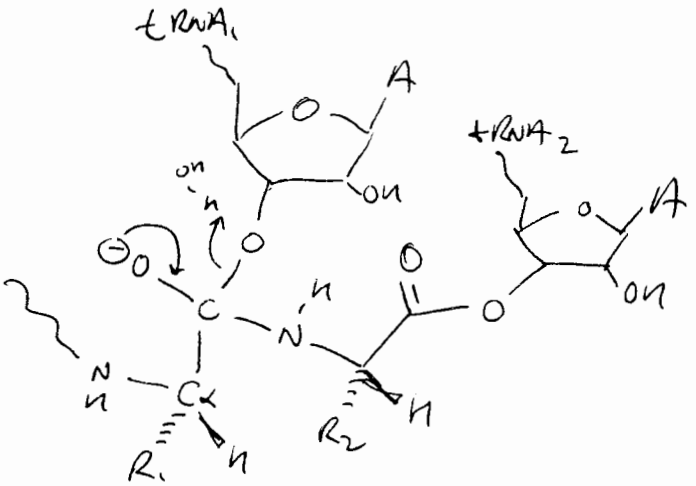
Difficult to draw because Pro is non-planar

Everything but the cis- proline = 13 pts total

(b; 5 pts) The structure below shows two charged tRNA molecules aligned for the process of peptide bond synthesis. Draw the first step of the reaction mechanism.

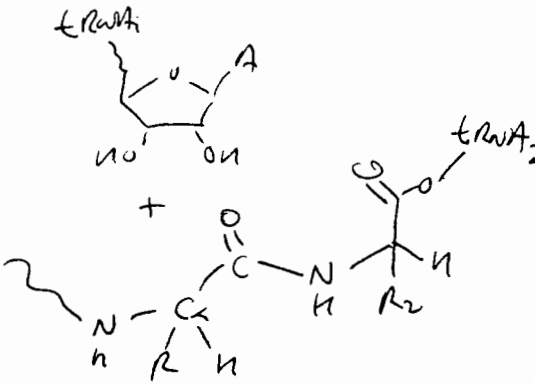


nucleophilic attack (+2)



(+3) tetrahedral intermediate

or = product (+2):



3. Thermodynamics (25 pts):

biological

(a; 6 pts) What are the two most important functions for lipids?

(+3)

- Biomembranes – phospholipids
- Fuel – fatty acids (+3)

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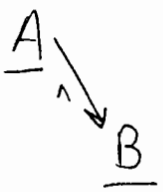
(b; 9 pts) Briefly describe how cells maintain order in the face of the universal tendency toward increasing entropy.

- Cells take in ordered molecules like glucose.
- They couple the favorable free energy of fuel oxidation (combustion) to the unfavorable decrease in entropy associated with biosynthesis, growth, and reproduction.
- The favorable catabolic reactions lead to production of CO_2 gas, with much greater entropy than glucose, and also heat (CO_2 is enthalpically very stable as well), which ↑ entropy of the universe. Don't need details of giving off CO_2 - just specify less ordered waste products.

+3 | (+1 or +2 for idea of coupling down + uphill)
+3 |
+3 |

(c; 10 pts) You have discovered an enzyme that converts substance A to substance B without requiring any input of free energy (i.e. the reaction proceeds without high-energy cosubstrates like ATP). The equilibrium lies far to the side of B. What then must be true about any process that carries out net conversion of B to A under the same conditions? Also, explain why your discovery either does or does not preclude the possibility that there may be a separate energy-consuming path for going from A to B, and a biological rationale for your answer.



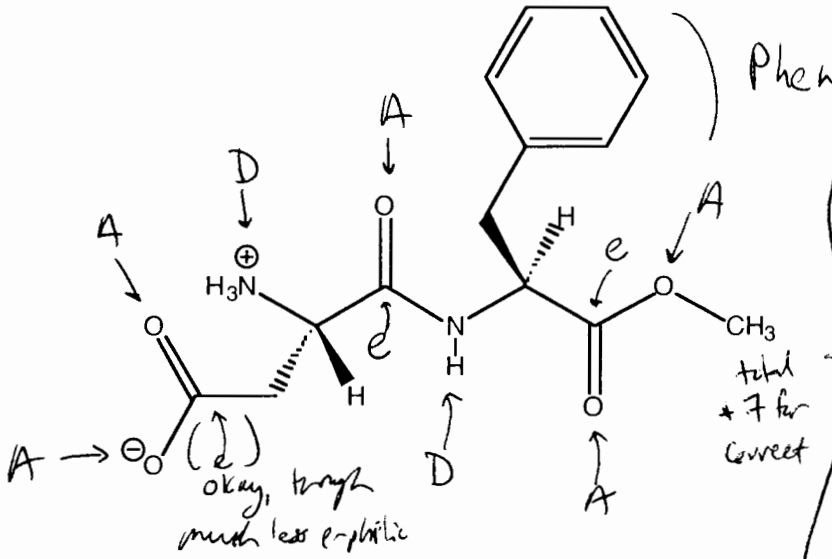
(+1) downhill → the reverse B → A process must be thermodynamically unfavorable, uphill. (+2)

(+3) Therefore B → A must be coupled to an exergonic reaction like ATP hydrolysis.

(+2) A → B can go via an energy-consuming back (drive the car downhill under power), would be done for greater speed, specificity, and/or control. (+2) for any one

4. Intermolecular interactions(22 pts):

(a; 12 pts) The structure of the artificial sweetener Aspartame is shown below. Identify potential hydrogen bond donors and acceptors, and electrophilic carbons. Why must phenylketonurics avoid Aspartame? (Memory jogger: would Aspartame absorb UV light?)



A = acceptor

D = donor

e = electrophile

Phenylalanine = Phe

+1 for ideal H-bonds

+2 for mostly correct D/A

+1 for correctly identifying all the D/A

+1 for no H-bond to aliphatic H's

+2 for electrophiles

– Aspartame is metabolized to give phenylalanine. PKU sufferers (+2) cannot convert Phe → Tyr, and so Phe & by-products accumulate. (+3)

+1 for Asp would absorb UV if missed PKU question

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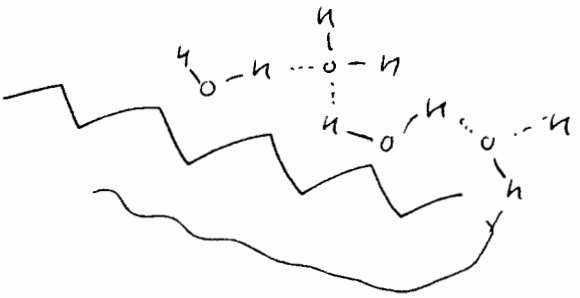
(b; 10 pts) Briefly describe the origin of the hydrophobic effect. Give the signs of ΔH°, ΔS°, and ΔG° for the process of dissolving a long alkyl chain in water.



(+3) – water forms an ordered cage around hydrophobic solutes. This is unfavorable – aggregation of the solutes (or phase separation)

(+2) leads to release of H2O into more disordered bulk water and is the driving force for the fact that oil and water don't mix.

(+2) ΔH° is (−) ~ the clathrate cage is enthalpically favorable!

(+1) ΔS° is (−) ~ because of ordering of water

(+2) $\Delta G^\circ = \Delta H - T\Delta S^\circ$ is (+) ~ process is not spontaneous

Score:	1.	pH, pK_a, and all that (25 pts):	_____
	2.	Amino acid and peptide bond structure and chemistry (26 pts):	_____
	3.	Thermodynamics (25 pts):	_____
	4.	Intermolecular interactions(22 pts):	_____
		Total: out of 100 (2 pts for Honor Pledge)	_____